REMARKS

Claims 15-17, 21-24 and 33 have been canceled. Thus, claims 34-45 remain pending for further prosecution in the present application. Based on arguments provided herein and the Sworn Declaration of Hansell H. Stedman submitted herewith, Applicants respectfully submit that the claims of the present application distinguish over the prior art of record and are in condition for allowance.

I. Claim Rejection - 35 USC §102(b)

In the non-final Office Action dated January 8, 2010, claims 21-24 are rejected under 35 USC §102(b) as being anticipated by U.S. Patent No. 6,776,771 B2 issued to van Moorlegem et al.

Claims 21-24 have been canceled. Accordingly, Applicants respectfully submit that this rejection can be withdrawn.

II. Claim Rejection - 35 USC §103(a)

A. *In the non-final Office Action dated January 8, 2010, claims 34-40 are rejected under 35 USC §103(a) as being obvious over U.S. Patent No. 5,728,066 issued to Daneshvar.*

The present invention relates to the field of gene therapy whereby a desired molecule is delivered into a target cell. More specifically, the present invention relates to facilitating the delivery of target molecules to a desired host muscle cell, such as cardiac muscle cells, while minimizing side effects. Thus, according to the present invention, the patient is rendered hypothermic, a region of the patient's microvasculature is isolated and exsanguinated (drained of

blood), and a macromolecular complex is delivered to the exsanguinated region under rapidly high hydrostatic pressure (in a range of 50mm Hg to 500mm Hg).

By way of example, a method of systemically transferring a macromolecular complex to muscle cells of a subject can include the steps of placing a patient under total circulatory arrest; lowering the patient's temperature to 12 to 18°C to render the patient hypothermic; isolating and exsanguinating a region of the patient; introducing a first balloon catheter and a second balloon catheter in cannulation sites, wherein upon inflation the first balloon catheters occludes the aorta and the second balloon catheter occludes the venae cavae; and infusing the macromolecular complex into the exsanguinated region under high hydrostatic pressure. The solution may also be allowed to dwell for a period of time (which may be for several minutes or longer) and is then flushed out of the exsanguinated region. The balloon catheters are removed, and the patient is resanguinated and rewarmed.

The above gene therapy method is particularly designed to avoid an immune response from circulating antibodies. The absence of circulating blood in the area to which the macromolecular complex is infused avoids contact with elements of the blood, such as cells, platelets, and tissue-reactive plasma components and minimizes the risk of inducing an immune response. The invention also avoids activation of various clotting factors and other factors that may interfere with the transfer of the macromolecular complex. Further, the present invention minimizes, or eliminates, exposure of other non-targeted areas of the body to the complex, such as exposure of the macromolecular complex to the liver or lungs of the patient.

The elected claims of the present application are directed to the structure of the balloon catheters referenced in the above method. In particular, independent claim 34 of the present

application is directed to an internal occlusion balloon catheter for occluding blood flow through an aorta of a hypothermic patient. A required structural limitation of the catheter of independent claim 34 of the present application reads, as follows:

> "... in an inflated condition, said balloon envelope forming an elongate, continuous, substantially-cylindrical tube along its full length, and when positioned within the patient's aorta, said full length of said tube of said balloon envelope being of sufficient length to extend continuously from a location adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding flow within the patient's entire aorta and preventing cross-flow through the aorta between various branch vessels branching from the aorta."

The catheter required by claim 34 facilitates compartmentalization of the circulation in the central and peripheral vascular systems. The central circulation (i.e., vessels directly supplying the thoracic and abdominal viscera) must be separated from the peripheral circulation (i.e., vessels supplying the skeletal muscles). When in the process of delivering a macromolecular complex to the heart, high venous pressure is applied and the inflated balloons transiently restrict flow of fluids between the peripheral and central circulations. Since the central vascular system includes vessels supplying the thoracic and abdominal viscera, vector transport to the abdominal viscera is minimized by restricting flow through the aorta and vena cavae, as they interconnect vessels supplying the thoracic and abdominal viscera.

Further, the catheter of claim 34 of the present invention is designed to be deployed solely when the patient is under total circulatory arrest, when the patient's heart is cooled to about 15 to 18°C, when the natural circulation rate is depressed to zero, and when cardiac circulation is isolated from the remainder of the patient's circulatory system. If the catheter is applied when the patient is warm under conditions of pulsed blood flow (as in Daneshvar discussed below), such deployment would be lethal within minutes because in the wake of sudden complete

circulatory collapse, tissue oxygen delivery would be inadequate to support mitochondrial ATP synthesis. However, in the present invention, the balloon which extends continuously from a location adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding flow within the patient's entire aorta, occludes fluid flow into and through the aorta and consequently occludes flow into and through branches interconnecting to the aorta.

For reasons stated below and in the Sworn Declaration of Hansell H. Stedman, Applicants respectfully submit that Daneshvar fails to disclose or render obvious to one of ordinary skill in the art a catheter having a balloon with the above referenced structural limitation; namely, an elongate, continuous, substantially-cylindrical tube balloon having a full length of sufficient length to extend continuously from a location adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding flow within the patient's entire aorta and preventing cross-flow through the aorta between various branch vessels branching from the aorta. Further, Daneshvar provides no useful teaching of catheters useful for gene therapy procedures.

Upon careful study of the disclosure provided by Daneshvar, it is clear that Daneshvar is not directed to gene therapy or for minimizing side effects with respect to gene therapy procedures. In addition, Daneshvar does not exsanguinate (drain blood from) a region of the patient into which a fluid is injected, does not render the patient hypothermic during the injection, and does not apply a macromolecular complex under rapidly applied high hydrostatic pressure to the exsanguinated region of the patient while preventing an immune response from circulating antibodies, contact with cells, platelets, and tissue-reactive plasma components of

blood, activation of various clotting factors and other factors that may interfere with the injected material, and exposure of other non-targeted areas of the body to the injected material such as the liver of lungs of the patient.

By way of example, on column 10, lines 31-34, Daneshvar discloses "the use of contrast media for the recognition of the anatomy of the aorta, its branches and the spaces of the heart which is referred to as cardiac catheterization or angiography of a vessel or its branches." Daneshvar further discloses a problem in that "during such an injection, commonly the contrast media quickly washes out by the rapid flow of the blood and this does not give enough chance for the observer to see the details of the area" (see column 10, lines 35-38). Thus, the invention of Daneshvar is directed to a catheter providing a momentary "resistance means" to be "created in front of the flow of the blood in the lumen of a vessel so that the speed of the blood in the vessel will decrease and this prevents the quick washout of the injected materials" (see Abstract). The primary goal of Daneshvar is to enable better monitoring or imaging of the flow of blood through the heart, not to prevent flow.

More specifically, Daneshvar discloses a balloon catheter for use in a warm patient (i.e. at normal body temperature) under pulsed blood flow conditions. The balloon is inflated for a short period of time sufficient only to momentarily re-direct blood flow in the heart so that the injected material (such as contrast media) remains in the heart for a longer period of time and flows through greater regions of the heart so that pulsed blood flow can be better monitored and imaged. The degree of resistance or occlusion can be as little as 10%. See column 14, line 4. In any case, pulsed blood flow is not prevented from passing through the heart and the patient is not placed under conditions of total circulatory arrest or hypothermic temperature. The Daneshvar

catheter is not designed to facilitate compartmentalization of the circulation in the central (i.e., vessels directly supplying the thoracic and abdominal viscera) and peripheral (i.e., vessels supplying the skeletal muscles) vascular systems. In addition, the catheter of Daneshvar does not minimize transport of blood flow and the injected material to the abdominal viscera by completely eliminating any flow through the aorta and vena cavae. Rather, in Daneshvar, the object is to provide improvements with respect to monitoring pulsed blood flow through the heart of the patient, not prevent it.

Daneshvar consistently refers to "blood" flow throughout the specification of the patent. For example, see blood flow described in: the Abstract; column 1, lines 14-15 and 41; column 4, lines 51-56; column 5, lines 59-60; column 6, lines 13-17; and column 7, lines 15-16 and 62-67. Accordingly, Daneshvar takes no steps in preventing contact of its injected fluids with the patient's blood and elements thereof as well as with organs such as the lungs and liver and with circulating antibodies. The reason for this is that Daneshvar simply relates to injecting contrast media for cardiac catheterization or angiography of a vessel or its branches and not to gene therapy. Thus, one of ordinary skill in the art relative to gene therapy, learns little to nothing from Daneshvar.

In the Office Action, the Examiner readily acknowledges that Daneshvar "does not disclose the balloon extending the length of the entire aorta." However, the Examiner concludes that this deficiency of the cited reference can simply be overlooked because "it would have been an obvious matter of design choice to a person of ordinary skill in the art to modify the balloon of Daneshvar".

Applicants respectfully submit it would not have been an obvious matter of design choice to a person of ordinary skill in the art to modify the balloon of Daneshvar such that the balloon would have a full length that extends continuously from a location adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding flow within the patient's entire aorta as well as collateral cross-flow into and out of branch vessels extending from the aorta.

It is well established that when a §103 rejection is based upon a modification of a reference that destroys the intent, purpose or function of the invention disclosed in the reference, such a proposed modification is not proper and a *prima facie* case of obviousness cannot be properly made. In re Gordon, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984).

As stated above and in the Sworn Declaration of Hansell H. Stedman, the intent, purpose and function of the balloon (4) of the catheter disclosed by Daneshvar is simply to provide a "resistance means" to be "created in front of the flow of the blood in the lumen of a vessel so that the speed of the blood in the vessel will decrease and this prevents the quick washout of the injected materials". Thus, the injected material of Daneshvar is injected directly into pulsed blood flow of a warm patient and the desire is to monitor the flow of blood through the heart, not to prevent flow. The intention of the catheter of Daneshvar is not to compartmentalize circulation in the central (i.e., vessels directly supplying the thoracic and abdominal viscera) and peripheral (i.e., vessels supplying the skeletal muscles) vascular systems and not to minimize transport of blood flow with injected material to the abdominal viscera by completely eliminating any flow through the aorta and vena cavae. Rather, the catheter of Daneshvar is merely to re-

direct blood flow through the heart by momentarily creating a resistance at a desired position. This prevents quick wash out of the injected materials.

For example, as explained on column 6, lines 13-20, of Daneshvar, the injection of contrast media into the left ventricle or inside the lumen of the aorta will result in the mixture of blood and contrast media to face resistance by the balloon of the catheter and to disperse in the space inside the ventricle and aorta due to the pulsed blood flow. This ensures the contrast media has needed time to fill the coronary and coronary bypass grafts with one injection and provides imaging with greater information.

As stated in the Sworn Declaration of Hansell H. Stedman, a balloon catheter having the structure required by claim 34 used for the intent, purpose and function of Daneshvar to inject contrast media or like fluid in the pulsed blood flow of a warm patient for purposes of providing resistance to blood flow would be instantly lethal. Accordingly, Applicants respectfully submit that one of ordinary skill in the art at the time of the present invention was made would have been aware that such a modification made to the catheter disclosed by Daneshvar would be instantly lethal when applied in accordance with the teachings of Daneshvar. The catheter of Daneshvar is clearly not meant to be lethal, and thus, modifying Daneshvar in a manner required by the claim 34 of the present invention would clearly destroy the intent, purpose and function of the catheter invention disclosed by Daneshvar.

Claim 34 of the present application is directed to an internal occlusion balloon catheter for occluding fluid flow through the aorta of a hypothermic patient and requires an inflatable and radially expandable balloon that, in an inflated condition within the aorta, forms an elongate, continuous, substantially-cylindrical tube along its full length continuously from a location

adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding blow flow within the patient's entire aorta. Thus, the homogenous distribution of force through the full length of the aorta occludes bulk flow through the aorta and prevents collateral cross-flow into and out of side branch vessels of the aorta. If the balloon of Daneshvar is enlarged/lengthened to extend continuously from a location adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding flow within the patient's entire aorta for purpose of preventing quick washout of injected material due to the speed of blood flow in a warm patient, one of ordinary skill in the art would be well aware that the deployment of such a balloon for the stated purpose in a warm patient under conditions of pulsed blood flow would result in the almost instantaneous fatality of the patient. Also, the purpose of the invention of Daneshvar is to permit flow of blood through the heart to be readily monitored, not prevented.

Accordingly, one of ordinary skill in the art would avoid modifying the balloon of Daneshvar in a manner that would be lethal to the patient and that would prevent the monitoring of pulsed blood flow through the heart of a warm patient. Thus, it would not be an obvious matter of design choice to provide the catheter of Daneshvar with the balloon as required by claim 34 of the present application.

For the above reason, Applicants respectfully submit that claim 34 is patentable and is not obvious to one of ordinary skill in the art based on the teachings of Daneshvar. Accordingly, Applicants respectfully request reconsideration and removal of the obviousness rejection of claims 34-40.

B. *In the non-final Office Action dated January 8, 2010, claims 41-45 are rejected under 35 USC §103(a) as being obvious over U.S. Patent No. 5,728,066 issued to Daneshvar in view of U.S. Patent No. 6,776,771 B2 issued to van Moorlegem et al.*

In the Office Action, Daneshvar is relied upon for rejecting the above referenced claims except with respect to limitations requiring balloon segments. Thus, van Moorlegem et al. patent is cited solely for this reason (i.e., merely for a disclosure of balloon segments).

Claim 41 depends from base independent claim 34. Thus, it is directed to an internal occlusion balloon catheter for occluding blood flow through an aorta of a hypothermic patient. A required structural limitation of the catheter of independent claim 34 of the present application reads, as follows:

> "... in an inflated condition, said balloon envelope forming an elongate, continuous, substantially-cylindrical tube along its full length, and when positioned within the patient's aorta, said full length of said tube of said balloon envelope being of sufficient length to extend continuously from a location adjacent a bottom of the patient's abdominal aorta through the patient's aortic arch and into the patient's ascending aorta thereby substantially filling and occluding flow within the patient's entire aorta and preventing cross-flow through the aorta between various branch vessels branching from the aorta."

Independent claim 42 requires an internal occlusion balloon catheter for occluding blood flow through a vena cavae of a hypothermic patient. A required structural limitation of the catheter of independent claim 42 of the present application reads, as follows:

> "... in an inflated condition, each of said series of balloons forming an elongate, continuous, substantially-cylindrical tube along its full length, and when positioned within the patient's vena cavae, one of said balloons being of sufficient length to extend continuously from a location adjacent a lower end of the patient's inferior vena cava to just below a right atrium of the patient's heart and another one of said balloons being of sufficient length to extend through the patient's superior vena cava and occlude the azygous vein but does not extend into the right atrium."

Applicants respectfully submit that the same arguments stated above with respect to the patentability of claims 34-40 over Daneshvar, also apply to the above referenced rejection when Daneshvar is combined with the van Moorlegem et al. patent. Modifying the catheter of Daneshvar relative to the limitations in claims 34 or 42 of the present application would destroy the intent, purpose and function of the catheters as they would result in instant fatality of the patient when used in accordance to the teachings of Daneshvar to monitor pulsed blood flow in a warm patient.

Van Moorlegem et al. disclose a dilation catheter that is used to widen a restricted blood flow passage. More specifically, van Moorlegem et al. disclose a dilation catheter for use in a procedure known as Percutaneous Transluminal Coronary Angioplasty (PTCA) for treating a patient having a stenosis (narrowing or constriction of the diameter of a bodily passage). During a PTCA procedure, the dilation catheter is used to increase the lumen by radial expansion of a balloon. An important teaching provided by van Moorlegem et al. with respect to their catheter is that:

> "If the inflated balloon obstructs blood for too long (typically for more than a few seconds), **permanent damage to downstream organs can occur** due to ischemia, which is the cessation of blood flow through the lumen. Accordingly, it is often desirable to **keep the patient's blood flowing through the lumen while the balloon is in the inflated state**. This is preferable to cycling the balloon between an inflated and deflated state, as such action can place additional stress on an already compromised lumen wall."

Accordingly, the catheters of both Daneshvar and van Moorlegem et al. are intended for deployment in a warm patient and under conditions of regular pulsed blood flow. Thus, as clearly stated in van Moorlegem et al., "if the inflated balloon obstructs blood flow for too long

(typically for more than a few seconds), permanent damage to downstream organs can occur." See column 1, lines 54-60, of the van Moorlegem et al. patent (and this is not even for a catheter deployed in the aorta or vena cavae).

Thus, one of ordinary skill in the art would be aware that modifying the prior art balloons used in warm patients under normal pulsed blood flow conditions as required to read on the claims of the present application and deploying these balloons in the aorta or vena cavae under conditions taught by Daneshvar and/or van Moorlegem et al., would be lethal. Thus, such combination and modification would be avoided and therefore would not be an obvious matter of design choice.

The experimental basis for the knowledge that complete occlusion of the great vessels is rapidly lethal is actually quite remote, and has not been replicated in the literature for many years because it is so firmly grounded in basic physiology. For this reason, today this demonstration would be considered an inappropriate use of animals in experimentation unless as part of a demonstration of a novel principle. Seminal papers in this field include the following:

Gibbon JH, Jr., Hopkinson M, Churchill ED (1932). Changes in the circulation produced by gradual occlusion of the pulmonary artery. *J Clin Invest*, 11:543. (This paper represents an experimental demonstration of the rapid lethality, in animal studies, of complete occlusion of flow through a great vessel.)

Churchil ED (1934). The mechanism of death in massive pulmonary embolism with comments on the Trendelenburg operation. *Surg Gynecol Obstet*, 59:513. (This paper by the same senior author incorporates the knowledge gained from the foregoing animal studies to explain why massive pulmonary embolism is so rapidly lethal in humans.)

Gibbon JH, Jr. (1937) Artificial maintenance of the circulation during experimental occlusion of the pulmonary artery. *Arch Surg*, 34:1105-1131. (This paper describes the breakthough observation that a mechanical pump oxygenator could briefly support the circulation and tissue oxygen delivery during complete occlusion of a great vessel.)

Gibbon JH, Jr. (1939). The maintenance of life during experimental occlusion of the pulmonary artery followed by survival. *Surg Gynecol Obstet*, 69: 602-614. (This paper extends the previous one by showing for a first time that survival is possible in a small mammal following transient occlusion of a great vessel while supporting the remainder of the circulation through a heart-lung device.)

Stokes TL and Gibbon JH, Jr. (1950). Experimental maintenance of life by mechanical heart and lung during occlusion of the venae cavae followed by survival. *Surg Gynecol Obstet*, 91: 138-156. (This paper set the stage for the entire clinical field of open heart surgery as we know it today, by showing for a first time that survival was possible if extraordinary means of circulatory support were used during transient complete occlusion of flow from venae cavae to heart in the normothermic mammal.)

As the catheters described in present application, when fully inflated, result in complete occlusion of the venae cavae and aorta along their entire length, even peripheral bypass by a pump oxygenator in the normothermic mammal would not support sufficient oxygen delivery to the central organs to support life. As a result, these catheters, by design, could only rationally be used under conditions of deep hypothermic circulatory arrest, as first described in the present application.

Accordingly, Applicants respectfully request reconsideration and removal of the obviousness rejection of claims 41-45 over the cited prior art combination.

III. Conclusion

In view of the above arguments and the Sworn Declaration of Hansell H. Stedman, Applicants respectfully submit that the rejections stated in the Office Action have been overcome. A favorable action on the merits is therefore requested.

Please charge any deficiency or credit any overpayment for entering this Amendment to our deposit account no. 08-3040.

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